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PATENT & TRADEMARK OFFICE
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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Attorney Docket No.: 3516.12US01

Pathak et al. Confirmation No.: 4146

Application No.: 10/010,715 Examiner: Mohamed, A.

Filed: November 9, 2001 Group Art Unit: 1653

For: BIOCOMPATIBLE CROSSLINKED POLYMERS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF

AMARPREET S. SAWHNEY

UNDER 37 C.F.R. § 1.132

This Declaration is submitted in support of the Amendment filed with the above-referenced patent application (the Application).

1. I, Amar Sawhney, and Chief Executive Office and a founder of Confluent Surgical, Inc., which is a licensee of the Application. Also, I am a scientist and an inventor for the Application, and am familiar with the materials and methods described for making and using the inventions in the Application. My curriculum vitae is attached.

2. I am also an inventor for U.S. Patent No. 5,410,016, which has been cited against the Application, and I am familiar with the formation of the hydrogels in U.S. Patent No. 5,410,016.

3. My areas of scientific knowledge include the subject matter claimed in the Application.

4. My areas of scientific knowledge include the subject matter discussed in patent 5,410,016 that relates to photoinitiation, and the role of dyes and catalysts or co-catalysts in the photoinitiation.

5. It is my opinion that the dyes used as photoinitiators in the photoinitiation process of the 5,410,016 patent are bleached during that process. After bleaching, the dyes are not effective for use as a visualization agent in the hydrogel. The dyes are used to absorb laser light that causes the dye to form a free radical to initiate photopolymerization. This process consumes the photoinitiator so that it is no longer effective as a dye. The dye is not a catalyst. The article authored by Gruber in Prog. Polym. Sci. (1992), previously submitted to the Examiner, clearly corroborates these facts, and, at page 954, states that the photoinitiator "is consumed during the initiation process".

6. In further support of this position, I have attached the Food and Drug Administration Premarket approval for FOCAL SEAL (the PMA). FOCAL SEAL is a product that is made according to teachings of the 5,410,016 patent, as corroborated by the fact that the label for FOCAL SEAL lists the 5,410,016 patent, see last page (page 33) of the PMA. Referring to page 29, FOCAL SEAL uses the dye EOSIN Y as a photoinitiator, see element "B - primer vial 2" and element "E", a syringe containing a solution including EOSIN Y. The EOSIN Y imparts a red or pinkish color to the powder ("pink", see element B) and the solution in the syringe ("pink", see element E). FOCAL SEAL, however, by a process of photopolymerization, forms hydrogel that is "clear", see PMA page 9, lines 3-4 and page 22, second paragraph. The "dye" becomes bleached during the photopolymerization process to produce a clear hydrogel.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 3/23/05

By

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EXPERIENCE:

July '98- Current: **Founder, President, and CEO, Confluent Surgical, Inc.:** Responsible for creation of company that is developing several innovative biosurgery products. SprayGel, the world's first synthetic post surgical adhesion barrier to be commercialized, and DuraSeal, a next generation synthetic surgical sealant. Raised $37MM for Confluent from venture capital sources.

Dec '96- July '98: **Director and Technology Founder, Focal Inc.:** Responsible for all new technology initiatives and new product development. Headed all Surgical Sealant Projects and Focal's scientific spokesperson for all clinical, regulatory, financial, and scientific audiences.

Aug '92 – Dec '96: **Senior Corporate Scientist and Technology Founder, Focal Inc.:** First scientist to join company. Co-inventor of core technology Headed development of and created the world's first synthetic sealant, FocalSeal, from concept to commercialization. Responsible for coordination of all research and development activity for this project, including preclinical safety and efficacy studies, project management, clinical trial site selection and execution, partnering negotiations, and next generation product research with external clinical and industrial collaborators. Recruited key individuals in materials and life sciences research teams.

Sept '87 - August '92: **Graduate Research Assistant, UT Austin-** Developed the following:

- Rapidly photopolymerizable biodegradable hydrogels for prevention of postoperative adhesions and for use as surgical adhesives. Served as a foundation for **Focal, Inc., a Lexington, MA** medical device company, now acquired by Genzyme.
- Hydrogel based drug delivery systems – Served as a foundation for **Infimed Therapeutics, a Cambridge, MA** biotech company.
- Photopolymerized PEG hydrogels for animal tissue encapsulation and conformal immunoprotective barriers. Served as a foundation for **Novocell a Santa Ana, CA** based biotech company.
- Synthesized a graft copolymer of poly(l-lysine) (PLL) and poly(ethylene oxide) for use in microcapsules showing enhanced biocompatibility.
- Synthesized and characterized biodegradable terpolymer and triblock copolymeric systems for the prevention of postoperative adhesions and the construction of a drug delivery device

OTHER APPOINTMENTS:

Chairman and Board Member – marketRx Inc.: A Bridgewater, NJ based company developing marketing automation and intelligence software, tools, and consulting services for the pharmaceutical industry.

Board Member – Access Closure, Inc.: A Palo Alto, CA based company developing therapies targeted to the management of vascular access for interventional radiology and cardiology applications.

General Partner – Incept, LLC: A Lexington, MA based company that serves as an enabler for healthcare entrepreneurial efforts.

EDUCATION:

University of Texas at Austin- Ph.D. in Chemical Engineering. Graduated August '92. Dissertation Title: Biocompatible microspheres and microcapsules for animal tissue encapsulation and transplantation. Advisor: Dr. J.A. Hubbell.

University of Texas at Austin- Master of Science in Chemical Engineering. Graduated May '89. Thesis Title: Biodegradable polymers for the prevention of postoperative adhesions. Advisor: Dr. J.A. Hubbell.

Indian Institute of Technology, Delhi- Bachelor of Technology in Chemical Engineering. Graduated May '87. Thesis Title: Design of a reverse osmosis plant for the treatment of sugar mill effluents.

AFFILIATIONS

American Institute of Chemical Engineers; American Chemical Society; Controlled Release Society; Society for Biomaterials; Tau Beta Pi, National Academy of Engineering.

PERSONAL

Wife: Deepika Sawhney, married for 9 years. Son, Anhad Singh Sawhney, 2 months.

PATENTS (Partial list)

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2. Sawhney A.S. and Hubbell J.A., "Biocompatible Microcapsules", *U.S. Patent No. 5,380,536.*
2. Hubbell A.S., Pathak, C.P., and Sawhney A.S., "Phototpolymerizable biodegradable hydrogels as tissue contacting materials and controlled release carriers", *U.S. Patent 5,410,016.*
3. Hubbell J.A., Pathak, C.P., Sawhney A.S and Desai, N.P., "Gels for encapsulation of biological materials", *U.S. Patent 5,529,914.*
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8. Hubbell J.A., Pathak, C.P., and Sawhney A.S., "Photopolymerizable biodegradable hydrogels as tissue contacting materials and controlled release carriers", *U.S. Patent 5,567,435.*
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17. Pathak, C.P., Sawhney, A.S. et al., "Apparatus, product and use related to intraluminal photothermoforming", *European Patent No.* 0 696 185 B1.
18. Sawhney, A.S., Melanson, D.M., et al., "Redox and photoinitiator priming for improved adherence of gels to substrates", *U.S. Patent 5,844,016.*
19. Sawhney, A.S. et al., "*Compliant tissue sealants" U.S. Patent 6,566,406.*
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11. Hubbell, J.A., Hill-West, J.L., Pathak, C.P., Sawhney, A.S., "PEG-based gels for the release of proteins and the encapsulation of cells", *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, **20**, 137-138, (1993).
12. Sawhney, A.S., Pathak, C.P., Cox, P.R., and Hubbell, J.A., "Conformal barriers by interfacial polymerization in contact with cells and tissue", *Polymer Preprints* **69**, 526 (1993).
13. Hill-West, J.L., Chowdhury, S.M., Sawhney, A.S., Pathak, C.P., Dunn, R.C., and Hubbell, J.A., "Prevention of postoperative adhesions in the rat by in situ photopolymerization of bioresorbable hydrogel barriers", *Obstetrics and Gynecology*, **83**, 59-64 (1994).
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17. Sawhney, A.S., Lyman, M.D., Jarrett, P.K., and Poff, B., "Evaluation of a photopolymerized hydrogel (FocalSeal) as a pneumosealant in a pulmonary dissection and bronchiopleural fistula model", *J. Surg.Res.*, (Submitted).
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Sawhney, A.S. and Drumheller, P.D., "Polymer Synthesis", in Frontiers in Tissue Engineering, C.W. Patrick, A.G. Mikos, and L.V. McIntire Eds., Elsevier Sciences.

INVITED AND CONFERENCE PRESENTATIONS (Not updated since 1998):

1. "Microcapsules with controlled permeability and enhanced biocompatibility", with J.A. Hubbell, *American Chemical Society*, Atlanta, GA, April 1991.
2. "Biocompatible microcapsules for in vivo transplantation of animal tissue", with J.A. Hubbell, *Society for Biomaterials*, Scottsdale, AZ, May 1991.
3. "Microcapsules for long term tissue immunoisolation", with C.P. Pathak and J.A. Hubbell, *American Institute of Chemical Engineers*, Los Angeles, CA, November 1991.
4. Sawhney, A.S., Pathak, C.P., Dunn, R.C., and Hubbell, J.A., "Prevention of postoperative adhesions using photopolymerizable biodegradable hydrogels", *Society for Gynecologic Investigation*, San Antonio, March 1992.
5. Pathak, C.P., Sawhney, A.S., Dunn, R.C., and Hubbell, J.A., "Photopolymerizable hydrogels for the prevention of postoperative adhesions", *Fourth World Biomaterials Congress*, Berlin, Germany, April 1992.
6. Sawhney, A.S., Pathak, C.P., and Hubbell, J.A., "Photocurable polyethylene glycol hydrogels for the immunoprotection of xenografted islets of langerhans", *Fourth World Biomaterials Congress*, Berlin, Germany, April 1992.
7. Sawhney, A.S., Pathak, C.P., Dunn, R.C., and Hubbell, J.A., "Modulation of adhesion between tissues by the application of adherent polymer gels: Prevention of postoperative adhesions", *Annual Meeting of the Biomedical Engineering Society*, Salt Lake City, Utah, October 1992.
8. Pathak, C.P., Sawhney, A.S., Cruise, G.M., and Hubbell, J.A., "Photocrosslinkable Hydrogels for the Encapsulation of Cells for Transplantation", *Annual Meeting of the Biomedical Engineering Society*, Salt Lake City, Utah, October 1992.
9. Sawhney, A.S., Hubbell, J.A., Pathak, C.P., Cruise, G.M., "Photocrosslinked hydrogels as encapsulants for xenografted cells", *American Chemical Society, Division of Colloid and Surface Chemistry*, Washington D.C., August, 1992.
10. Sawhney, A.S., Pathak, C.P., Dunn, R.C., and Hubbell, J.A., "Prevention of postoperative adhesions in a rabbit uterine horn model using a photopolymerizable biodegradable precursor", *48th Annual Meeting of the American Fertility Society*, New Orleans, November 1992.
11. Pathak, C.P., Sawhney, A.S., and Hubbell, J.A., "Photopolymerizable degradable hydrogel adhesives", *American Institute of Chemical Engineers*, Miami, November 1992.
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13. Hubbell, J.A., Hossainy, S.F.A., Pathak, C.P., Sawhney, A.S., Slepian, M.J., "Gels for the reduction of thrombogenicity of the vessel wall", *American Association of Medical Instrumentation*, Bethesda, December, 1992.
14. Hill, J.L., Sawhney, A.S., Pathak, C.P., Hubbell, J.A., "Prevention of post-operative adhesions using biodegradable hydrogels", *Society for Biomaterials*, Birmingham, April, 1993.
15. Slepian, M.J., Hossainy, S.F.B., Pathak, C.P., Sawhney, A.S., Massia, S.P., and Hubbell, J.A., "Bioerodible endovascular gel paving: a new paving from for the reduction of thrombogenicity of injured arterial surfaces", *Society for Biomaterials*, Birmingham, April, 1993.

16. Cruise, G.M., Sawhney, A.S., Pathak, C.P., Luther, K.M., Hubbell, J.A., "Poly(ethylene glycol) based conformal coatings as permselective membranes for transplantation", *Society for Biomaterials*, Birmingham, April, 1993.
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21. Slepian, M.J., Massia, S.P., Sawhney, A.S., Pathak, C.P., Berrigan, K., Roth, L., and Hubbell, J.A., "Endoluminal gel paving using in situ biodegradable photopolymeized hydrogels: acute efficacy in the rabbit", *American Heart Association*, Atlanta, November, 1993.
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GUEST REVIEWER:

1. Biomaterials
2. Journal of Biomedical Materials Research
3. Journal of Biomaterials Science
4. Biotechnology and Bioengineering

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 26 2000

Ms. Mary Lou Mooney
Director, Regulatory Affairs
Focal, Inc.
Four Maguire Road
Lexington, Massachusetts 02173

Re: PMA 990028
FocalSeal-L Synthetic Absorbable Sealant
Dated: June 4, 1999
Filed: June 7, 1999
Amended: September 9 and December 1, 1999, January 27, March 30 and 31, April 20 and May 10 and 19, 2000

Dear Ms. Mooney:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the FocalSeal-L Synthetic Absorbable Sealant. This device is indicated for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include the results of continued study of cancer recurrence in patients enrolled in your US study. This additional condition of approval is to further evaluate the cancer recurrence rates observed in your U.S. study, i.e., 13/125 (10.4%) for FocalSeal Sealant versus 4/55 (7.3%) for control patients. Please submit by June 26, 2000, a supplement containing a five year protocol for studying cancer recurrence in the patients enrolled in your U.S. study.

Expiration dating for this device has been established and approved at: 1) 23 months at –20°C for Primer Vial 1, 2) 27 months at –20°C for Primer Vial 2, 3) 15 months at –20°C for the Sealant Syringe and 4) 24 months at room temperature for the product applicators.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by

FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Charles N. Durfor, Ph.D. at (301) 594-3090.

Sincerely yours,

Philip J. Phillips
Deputy Director for Science and
Regulatory Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b)has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: SURGICAL SEALANT

Device Trade Name: FOCALSEAL-L SYNTHETIC ABSORBABLE SEALANT

Applicant's Name and Address: Focal, Inc.
Four Maguire Road
Lexington, MA 02421

Date of Panel Recommendation: May 8, 2000

Date of GMP Inspection: March 6-10, 2000

Premarket Approval Application Number: P990028

Date of Notice of Approval to the Applicant: May 26, 2000

Expedited Review: Expedited review was granted on March 25, 1999 based on the potential public health benefit from reducing the number of patients experiencing air leaks through hospital discharge following pulmonary resection.

II. Indications for Use

FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

III. Device Description

The FocalSeal-L Surgical Sealant system is comprised of synthetic absorbable sealant and primer solutions, two syringe/applicators, a light source, light wand and a PowerCap® light tester. The Sealant is formed via chemical and photochemical polymerization processes. The Sealant solution is provided in frozen form packaged in a red syringe and two primer vials. The two syringe applicators are used to deliver the primer and sealant solutions to the target tissue site. The FocalSeal reusable light source and light wand, ordered separately, photopolymerize the sealant solution to a thin film hydrogel. FocalSeal-L primer and sealant are aqueous solutions of poly (ethylene glycol) that have been modified with short segments of acrylate-capped poly (L-lactide) and poly (trimethylene carbonate). These solutions also contain buffers, initiators, and stabilizers.

FocalSeal-L Surgical Sealant solutions (i.e., primer and sealant) are applied to the target tissue site as liquids. Upon exposure of the photo-initiator, Eosin-Y, to blue-green light, the primer and sealant solutions polymerize to form a crosslinked, clear, flexible, adherent hydrogel network. The sealant expands upon contact with body fluids and reaches its equilibrium swell volume within 24 hours. Over time the poly (L-lactide) and poly (trimethlyene carbonate) segments of FocalSeal-L Surgical Sealant degrade by hydrolysis, causing loss of mass and structural integrity. This results in the eventual dissolution and clearance of the Sealant via water-soluble molecules that are cleared through the kidneys or locally metabolized.

IV. Contraindications

- FocalSeal-L Sealant is contraindicated for patients undergoing pneumonectomy or application over open or closed defects in main stem or lobar bronchi, due to an increased incidence of broncho-pleural fistulae observed in clinical study patients undergoing sleeve resection or bronchoplasty.
- FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.

V. Warnings and Precautions

Warnings and Precautions can be found in the product labeling.

VI. Alternative Practices or Procedures

Surgical procedures for airleak cessation with and/or without use of autologous tissue, for example, air leak oversew or overlay with pleural tent. Products made of glutaraldehyde-crosslinked bovine pericardium or collagen are applied as patches or strips over tissue sites to reduce or eliminate air leaks.

VII. Potential Adverse Effects of the Device on Health

Adverse events which occurred in the FocalSeal-L cohorts at an incidence of 1% or greater in the US study and 2.9% or greater in the European study are listed in Tables 1 and 2, respectively. The adverse events are listed in descending order according to frequency. These tables list all adverse events reported in the study including those attributed and not attributed to treatment.

Summary of Adverse Events for U.S. Study
Table 1

	FocalSeal-L (n=125)		*Control (n=55)*	
Event	#	%	#	%
Arrhythmia	29	23.2	17	30.9
Fevers	15	12.0	8	14.5
Cancer Progression	13	10.4	4	7.3
Pneumothorax	10	8.0	4	7.3
Thoracic Wound Infection	9	7.2	2	3.6
Pneumonia	9	7.2	5	9.1
Death	7	5.6	4	7.3
Confusion	7	5.6	0	0
Upper Respiratory Infection	7	5.6	3	5.5
Anemia	6	4.8	5	9.1
Ileus / Intestinal Obstruction	5	4.0	2	3.6
Urinary Tract Infection	4	3.2	3	5.5
Empyema	4	3.2	0	0
Persistent Atelectasis	4	3.2	0	0
Pulmonary Emboli	3	2.4	0	0
Deep Vein Thrombosis	3	2.4	0	0
Pleural Effusion	3	2.4	0	0
Residual Space	3	2.4	0	0
Colitis / Gastroenteritis	3	2.4	0	0
Hemoptysis	2	1.6	0	0
CHF	2	1.6	0	0
COPD	2	1.6	0	0
Anxiety	2	1.6	2	3.6
Hypotension	2	1.6	0	0

In the U.S. clinical trial, 7/125 FocalSeal-L and 4/55 Control patients died during the time patients were on study. All deaths were judged as not related to treatment by the investigators. Regarding the severity of non-fatal adverse events, there were 66 severe events in 43 (34%) patients, 90 moderate events in 72 (58%) patients and 27 mild events in 13 (10%) of the 125 FocalSeal-L patients. In the 55 control patients there were 30 severe events in 17 (31%) patients, 41 moderate events in 28 (51%) patients and 15 mild events in 4 (7%) patients.

Summary of Adverse Events for European Study
Table 2

Event	*FocalSeal-L (n=34)*	*Control (n=26)*
Bronchial Fistulae [associated events included infection (4) and pneumothorax (2)]	8 (23.5%)	0 (0%)
Out of Range Lab Values	6 (17.6%)	2 (5.9%)
Pneumonia	5 (14.7%)	1 (3.8%)
Bronchial Infection	5 (14.7%)	0 (0%)
Superficial Phlebitis	4 (11.8%)	0 (0%)
Death	2 (5.9%)	1 (3.8%)
Metastatic Disease	2 (5.9%)	1 (3.8%)
DVT	2 (5.9%)	0 (0%)
Pneumothorax	2 (5.9%)	1 (3.8%)
Respiratory Depression / Insufficiency	2 (5.9%)	1 (3.8%)
Fever and Leukocytosis	1 (2.9%)	2 (7.7%)
Urinary Tract Infection	1 (2.9%)	2 (7.7%)
Pulmonary Infiltrates	1 (2.9%)	1 (3.8%)
Cardiac Failure	1 (2.9%)	1 (3.8%)
Cardiac Tamponade	1 (2.9%)	1 (3.8%)
Hematoma	1 (2.9%)	1 (3.8%)
Pulmonary Embolism	1 (2.9%)	1 (3.8%)
Anemia	1 (2.9%)	1 (3.8%)
Sepsis	1 (2.9%)	1 (3.8%)

The following events occurred in one FocalSeal-L patient, but no control patients: pulmonary erosion, post-thoracotomy syndrome, effusion, atelectasis, bronchitis, pulmonary edema, arrhythmia, lymphedema, intestinal obstruction, visual field defect, CVA, and vomiting.

In the European clinical trial, 2/34 FocalSeal-L and 1/26 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment.

The only remarkable clinical event finding in the European study was the higher than expected (23.5%) incidence rate of bronchial fistulae (8/34 treated patients). Other relevant details were that the fistulas all occurred at the bronchial stump and that 7/8 of the bronchial fistulas occurred in patients who had FocalSeal-L Sealant applied to the bronchial stump. Analysis concluded that the FocalSeal-L Sealant, when applied to the bronchial stump site, acted as a mechanical barrier to adjacent tissue overlap and adhesion attachment, thereby eliminating a natural source of revascularization, resulting in slower healing. Since this only occurred in approximately one third of patients who had FocalSeal-L Sealant applied to the bronchial stump, it is believed that application of FocalSeal-L Sealant to the stump was one of several contributing factors which may lead to bronchial fistulae formation. Other known risk factors include: extent of resection; sleeve resections; age greater than 60 years; prolonged post-operative ventilation and diabetes.

VIII. Marketing History

FocalSeal-L Sealant was granted the CE Mark for commercial distribution throughout the European Union in December, 1997. Sales have commenced in the European Union countries as well as in Canada, Australia, New Zealand, South Africa, Egypt, Hong Kong, Israel and Switzerland. FocalSeal-L Sealant has not been withdrawn from any market for reasons relating to the safety and effectiveness of the device.

IX. Summary of Preclinical Studies

The preclinical studies with FocalSeal-L demonstrated that device extracts are non-cytotoxic and a moderate irritant. The genotoxicity studies indicated that under some circumstances mutation of mammalian cells (mouse lymphoma mutation assay) was observed. Implantation studies indicated that the device degrades very slowly. A chronic inflammatory response was observed with macrophages and giant cells and palpable tissue site in 90 day studies. At the last test time point of 600 days, the device was almost completely resorbed. In this same long-term study in rats, tumors were observed in treated and historical control animals with a similar frequency and time course. Summaries of the preclinical tests performed on FocalSeal-L Sealant are presented in the following Tables: biocompatibility testing (Table 3), laboratory performance testing (Table 4) and animal performance testing of FocalSeal-L Sealant (Table 5).

Table 3 - Biocompatibility Testing Summary for FocalSeal-L Sealant[1]

Type of Test	Method	Result
Cytotoxicity	USP <87> Agar Diffusion (*in vitro*); MEM extract	Non-cytotoxic
Sensitization	Kligman Maximization Test (guinea pig); saline extract	Non-sensitizing
Irritation	USP Intracutaneous Injection (rabbit); saline extract	Moderate irritant

Acute Systemic	Systemic Injection (mouse); saline extract	Non-toxic
Subchronic Toxicity/ Implantation	Intra-Peritoneal Implant (rat) for 8 Days, 30 Days and 14 Weeks	Non-toxic, but chronic inflammation observed at 30x the clinical dose
Chronic Toxicity/ Implantation	Intra-Peritoneal Implant (rat) for 26 Weeks	Non-toxic, but chronic inflammation observed at 50x the clinical dose
Genotoxicity	Ames Mutagenicity (*in vitro*); DMSO extract	Non-mutagenic
	Mouse Lymphoma Cell Mutation Assay (*in vitro*); saline and DMSO extracts[2] (in accordance with ASTM E1280-97)	Non-mutagenic after 4 hrs Weak mutagen after 24 hrs incubation
	Chinese Hamster Ovary (CHO) Chromosomal Aberrations Assay (*in vitro*); saline and DMSO extracts[2]	Non-mutagenic
Implantation	Intramuscular (rat) for 601 days[2]	Encapsulation; small amount of material remaining; local macrophage response
	Application to Resected Lung Tissue (dog) for 8 Months[2]	Encapsulation; localized macrophage response
	Application to Resected Lung Tissue (dog) for 16 Months[2]	Encapsulation; localized macrophage response
Hemocompatibility	Hemolysis Study in Rabbit Whole Blood (*in vitro*); saline extract	Non-hemolytic
Pyrogenicity	USP<151> Pyrogen Test (rabbit); saline extract	Non-pyrogenic

[1] Testing was performed on polymerized and non-polymerized samples unless otherwise noted.
[2] Testing was performed on polymerized samples.

Table 4 – Laboratory Performance Testing of FocalSeal-L Sealant

Test	Methodology	Results

Seal Pressure	FocalSeal-L Sealant was applied to a latex substrate containing a 2 mm diameter hole. The latex sustrate was pressurized to failure.	Mean seal pressure of 257 cm H_2O
Elongation	Polymerized FocalSeal-L Sealant samples were placed into Instron test fixture and stretched to failure.	Mean elongation of 1568 % strain

Table 5 – Animal Performance Testing of FocalSeal-L Sealant

No. of Studies	Methodology	Results
3	Thoracotomy procedure and apical amputation of the cranial, middle and caudal lobes in dogs. FocalSeal-L Sealant was applied over each staple line and lung was inflated to confirm sealing effectiveness. Tissue adherence was assessed 2 weeks following surgery using a predefined 0 – 4 scoring system. The acceptance criterion was a score of ≥ 2.5.	Study 1 - all scores ≥ 3.0 Study 2 - all scores ≥ 3.0 Study 3 - all scores ≥ 3.0

X. Summary of Clinical Studies

The following is a summary of the large-scale study designed to support approval. At the conclusion of this description is a brief summary of an uncontrolled clinical study performed in Europe.

U.S. Study

The study was open label, prospective, randomized, multi-center study comparing standard tissue closure techniques (control) to standard tissue closure techniques plus the FocalSeal-L Sealant (treatment) in patients scheduled to undergo elective pulmonary resections via an open thoracotomy procedure. Application of FocalSeal-L Sealant to the bronchial stump was contraindicated in this study. The study enrolled patients in a 2:1 randomization scheme of treated to control patients. There were 125 FocalSeal-L and 55 control patients in the safety cohort. Because the first two FocalSeal-L patients were prospectively identified as pilot patients and not included in the effectiveness analysis, there were 172 subjects in the effectiveness cohort (i.e., 117 FocalSeal-L and 55 control patients). Patient enrollment was also stratified with respect to a high or low risk for adverse events based on pre-operative and intraoperative risk factors.

FocalSeal-L Sealant was applied after patients had received standard surgical management with or without an attempt to close air leaks with conventional sutures

and/or staples. The device was applied by first brushing the primer solution onto the tissue site. Second, the sealant solution was brushed onto the target tissue with the sealant applicator mixing the primer and sealant solutions. The combination of the sealant and the primer solutions resulted in a free radical chemical reaction between the primer and sealant solutions that caused partial polymerization. Third, the sealant solution was dripped onto the target tissue and then illuminated to further photo-polymerize the device.

Control Therapy:
Patients randomized to the control group received standard surgical management, with or without attempted additional closures of air leaks, per surgical routine, i.e., conventional suture and/or staple closure.

Study Endpoints:
The primary efficacy endpoint was the proportion of patients determined to be air leak free at the end of the surgical procedure and who remained air leak free through hospital discharge. The secondary efficacy endpoints were mean time to air leak cessation and the proportion of patients air leak free at the end of the surgical procedure. Data concerning the time to chest tube removal and the time to hospital discharge were also collected. Device safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1, 3 and 6 months post-operatively.

Listing of Study Centers and Patient Treatment Group Assignment:
The study enrolled and treated 125 FocalSeal-L and 55 control patients. The study results from all of these patients were included in considerations of product safety. The product effectiveness cohort excluded the first two FocalSeal-L patients enrolled at each center. Thus, the dataset for effectiveness includes 172 patients (i.e., 117 FocalSeal-L and 55 control patients).

Study Results:

Baseline Demographics:
The study population primarily consisted of cancer patients undergoing surgery for tumor resection. The most common primary indication for surgery in both groups was pulmonary cancer, (see Table 6). The majority of the demographic factors were the same for both treatment arms (e.g., gender, race, and age). The only demographic factor approaching a statistically significant difference was the incidence the FEV/FVC% < 65%, (i.e., FocalSeal-L 26/125 (21%) versus Control 19/55 (35%) p = 0.064). The surgical resection procedures for both groups were also similar.

Table 6 - Patient and Baseline Characteristics[1]

		FocalSeal-L (n=125)	Control (n=55)
Gender	Female	73 (58%)	24 (44%)
	Male	52 (42%)	31 (56%)
Age at Surgery (yrs)	Mean	62.1	62.1

	Range	31 – 75	21 – 75
	Std. Dev.	9.7	10.0
Primary Surgical Diagnosis	Pulmonary Cancer	90 (72%)	43 (78%)
	Pulmonary Metastasis	16 (13%)	7 (1%)
	Benign Neoplasis	8 (7%)	2 (4%)
	Other	11 (9%)	3 (5%)
Types of Surgery	Single Lobectomy	83 (66%)	28 (51%)
	Single Wedge	18 (14%)	7 (13%)
	Segmentectomy	8 (7%)	6 (11%)
	Bi-Lobectomy	8 (7%)	4 (7%)
	Other	8 (7%)	10 (18%)
Number of Patients with Air Leaks Prior to Randomization		95 (76%)	39 (71%)

[1]No statistically significant ($p<0.05$) differences were detected between groups.

As illustrated in Table 7, the treatment groups were also balanced with regard to risk stratification.

Table 7 - Risk Factors

	FocalSeal-L	Control	p-value
Fragile Tissue	28/125 (22%)	10/55 (18%)	0.647
Extent of Surgery	21/125 (17%)	14 (25%)	0.099
Surgical sites ≥ 4	38 (30%)	21 (38%)	0.268
Low risk (Score 0-4)	110 (88%)	46 (84%)	
High risk (score 5-8)	15 (12%)	9 (16%)	
Mean risk score	2.4	2.7	

Effectiveness Analysis:
FocalSeal-L Sealant use as an adjunct to standard surgical management of pulmonary airleaks, i.e., conventional suture and/or staple closure provided a statistically significant increase in the proportion of patients air leak-free from time of skin closure through hospital discharge (the primary study endpoint) as well as: 1) a reduction in the time to air leak cessation and 2) an increase in the proportion of patients air leak free at the end of surgery (i.e., the secondary endpoints). These data are displayed below in Table 8. Analyses of the Time to Chest Tube Removal and the Time to Hospital Discharge revealed no statistically significant differences between the two treatment groups (Table 9).

Table 8
Primary and Secondary
Study Endpoint Data

	FocalSeal-L (n=117)	Control (n=55)	p-Value
Patients Air Leak-Free through Hospital Discharge	39% (46/117)	11% (6/55)	0.001[1]

Patients Air Leak-Free at Skin Closure	92% (108/117)	29% (16/55)	0.001[1]
Time to Air Leak Cessation (Hrs)			0.006[2]
Mean (SE)	30.9 (4.8)	52.3 (11.6)	
Median	12.1	27.6	

[1] Mantel-Haenszel Test
[2] Generalized Wilcoxon Test comparing time to last air leak distribution

Table 9 - Additional Analyses

	FocalSeal-L (n=125)	Control (n=55)	p-Value[1]
Days to Chest Tube Removal			
Mean (SE)	4.5 (0.2)	5.2 (0.5)	NS[1]
Median	4.0	4.0	
Days to Hospital Discharge			
Mean (SE)	7.4 (0.4)	10.1 (1.8)	NS
Median	6.0	6.0	
Days to Drainage < 125 cc/day			
Mean (SE)	3.4 (0.12)	3.7 (0.25)	NS
Median	3.0	3.0	
Patients with Recurrent Air Leak	62/108 (57%)	10/16 (63%)	NS

[1] NS – Not statistically significant.

Airleak cessation – For the entire effectiveness cohort, the incidence of patients being air leak-free from the end of surgery through hospital discharge (i.e., the primary study endpoint) was 46/117 (39%) for FocalSeal-L and 6/55 (11%) for Control patients, which was statistically significant (p=0.001) by the Mantel-Haenszel Test. For the entire effectiveness cohort, the frequency of patients that were air leak-free at the end of surgery (i.e., a secondary study endpoint) was 108/117 (92%) and 16/55 (29%) for FocalSeal-L and Control patients, respectively, which was statistically significant (p=0.001) by the Mantel-Haenszel Test. For the subset of patients who were airleak free at the end of surgery (see below), the proportion who remained airleak free through hospital discharge was 46/108 (42.6%) for FocalSeal-L and 6/16 (37.5%) for Control patients. This difference was not statistically significant.

Airleak recurrence - The percent of patients who were air leak free at skin closure, but subsequently developed a post-operative air leak was comparable between the FocalSeal-L (57%) and Control (63%) groups. For both study groups, the majority of the air-leaks developed during the first 24 hours after surgery, i.e., 93% for FocalSeal-L 90% for Control patients.

High/Low Risk Patients - For patients in the low risk stratum, 42/102 (41%) FocalSeal-L and 5/46 (11%) Control patients were air leak-free from the time of skin closure through hospital discharge. For patients in the high risk stratum, 4/15 (27%) FocalSeal-L and 1/9 (11%) control patients were air leak-free from the time of skin closure through hospital discharge.

Device Safety

Study Withdrawals:
No patients withdrawals occurred during the 6 month study. 13 (8%) patients were lost to follow-up. Per treatment arm, the division was 6 (5%) FocalSeal-L and 7 (13%) control patients.

Adverse events: Are displayed in section VI.

There were no reports of unanticipated adverse device effects in the study, (where an adverse device effect was defined as a serious adverse event which was probably or definitely related to the device and which had not been previously identified in the clinical investigation or the study protocol).

Patient Deaths – 7/125 (5.6%) FocalSeal-L and 4/55 Control (7.2%) patients died during the study. All deaths were judged by investigators as not related to treatment. Causes of death are displayed in Table 10.

Table 10
Causes of Death for Patients in the US Study
(All deaths were judged as not related to treatment by investigators)

FocalSeal-L Patients	Control Patients
Pneumonia (before discharge)	Pneumonia (before discharge)
Acute respiratory distress (before discharge)	Respiratory failure (betwx 1-3 mo. visit)
Metastatic disease in spine & liver (betwx 1-3 mo. visit)	Recurrent cancer (betwx 3-6 mo. Visit)
Cardiac disease (betwx 3-6 mo. visit)	Metastatic cancer progression (after 6 month visit)
Metastatic cancer progression (betwx 3-6 month visit)	
Metastatic cancer progression (after 6 mo. Visit)	
Metastatic cancer progression (after 6 mo. Visit)	

European Study

Study Design:
An open-label, prospective, randomized study was conducted in 34 FocalSeal-L and 26 Control patients undergoing lobectomy or segmental lung resection at 2 European clinical sites. Patients were over 18 years old, with SGPT, SGOT and alkaline phosphatase levels < 1.5 ULN; Bilirubin < 1.5 mg/dL; creatinine < 2.0 mg/dL; hematocrit > 25%, PT < 15 sec and a negative pregnancy test. Patients were excluded from study entry if they were: scheduled for pneumonectomy or presented with extensive intrathoracic pathology such as wide spread tumor or extensive adhesions from previous thoracic trauma or surgery; pregnant or lactating; with a history or lab evidence of hemostatic abnormality or failure to achieve adequate hemostasis at surgery; severe congestive heart failure, COR pulmonale and/or renal failure or the patient underwent investigational therapy within 28 days before surgery or planned treatment within next 30 days.

The primary efficacy endpoint was the proportion of patients air leak free at the end of the surgical procedure. The severity of air leaks was scored 0-3 (0= no leak, 1= just detectable in underwater test, 2= easily detectable in underwater test and 3= measurable) by the anesthesiologist. Patients were followed for 2 months. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1 and 2 months post-operatively.

Study Results:

Baseline Demographics:
The study population was predominantly male (i.e., 70% and 77% for FocalSeal-L and Control groups, respectively) and the primary surgical diagnosis was bronchogenic carcinoma (i.e., 77% and 65% for FocalSeal-L and Control groups, respectively). The primary surgical procedure was single lobectomy (i.e., 83% and 77% for FocalSeal-L and Control groups, respectively).

Effectiveness Analysis:
The proportion of patients air leak free at the end of the surgical procedure was 100% in the treatment group and 27% in the control group (p=0.001).

Safety Results:
13 treatment patients experienced 1 or more clinical events including pneumonia, fistula, empyema, pneumothorax, pleural effusion, lung hematoma, DVT, and sepsis. One FocalSeal-L patient died due to cardiac failure. All clinical events were managed using standard medical and/or surgical therapy. A table of the adverse events in presented in Section VI.

XI. Conclusions Drawn from Study

The results of the U.S. study demonstrated a significantly greater proportion of FocalSeal-L patients were air leak-free at the end of the surgical procedure and remained air leak-free through hospital discharge when compared to Control patients ($p=0.001$). The mean time to air leak cessation was significantly shorter in the FocalSeal-L Sealant group ($p=0.006$) and a statistically significant reduction in intraoperative air leaks was observed in the FocalSeal-L Sealant group when compared to the Control patients.

The FocalSeal-L Sealant group showed trends toward a shorter duration of chest tube placement and a shorter length of hospital stay. These improvements were not statistically significant.

There were no statistically significant differences in the incidence of adverse events between the FocalSeal-L Sealant group and the control group.

These results support the safety and effectiveness of FocalSeal-L Sealant when used as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

XII. Panel Recommendations

On May 8, 2000, the General and Plastic Surgery Devices Panel recommended approval with conditions for Focal, Inc.'s PMA for FocalSeal-L Sealant. In these discussions the Panel considered the adequacy of the preclinical testing. The Panel voted against requiring additional animal testing to evaluate the carcinogenicity of the device. The Panel also discussed the clinical significance of the elevated incidence of thoracic wound infection and empyema that were observed in the US study. Regarding tumor progression, the Panel stated that the incidence of tumor progression in the study was acceptable. While some Panel members were satisfied with the 6 month follow-up of patients in the US study, other Panel members believed that longer patient follow-up (e.g., 2-5 years) would be appropriate to see if there is an impact on cancer progression. The Panel voted in favor of collecting additional postmarket data on the incidence of infection and cancer progression.

Regarding product effectiveness, the Panel determined that the data in P990028 demonstrate a reasonable assurance that the use of the FocalSeal – L Sealant in a significant portion of the target population will provide clinically significant results. The Panel also commented on the similar incidence of air leak recurrence for FocalSeal-L (62/108 (57%)) and control (10/16 (63%)) patients. The Panel concluded that patients receiving FocalSeal-L displayed statistically significant improvements in the incidence of being air leak-free: 1) from the time of skin closure through hospital discharge and 2) at the end of surgery as well as a 3) reductions in the time to air leak cessation for

FocalSeal-L patients, but statistically significant improvements in the times to Chest Tube Removal, Hospital Discharge or Drainage < 125 cc/day were not observed.

XIII. CDRH Decision

Expedited review was granted on March 25, 1999 based on the potential public health benefit of FocalSeal-L Sealant for reducing the number of patients experiencing air leaks through hospital discharge following pulmonary resection.

Inspection of the sponsor's manufacturing facilities was performed on March 6-10, 2000. The facility was found to be in compliance with the device Good Manufacturing Practice regulations on May 26, 2000.

The FDA reviewed the recommendations provided by the General and Plastic Surgery Devices Panel at the May 8, 2000 Panel meeting. With regard to the impact of device use on the incidence of thoracic wound infection and empyema, FDA determined that the clinical experience from the U.S. and European studies was sufficient to accurately describe these adverse events in separate Warning statements in the product labeling. These statements would clarify the existing knowledge about the incidence of wound infection and empyema. Regarding the impact of device use on the incidence of cancer progression, the FDA determined that the sponsor should continue to evaluate the incidence of cancer emergence or recurrence in all (i.e., both FocalSeal-L Sealant and Control) patients who enrolled in the U.S. clinical study with annual visits up to 5 years post-surgery and FocalSeal-L implantation.

FDA issued an approval order on May 26, 2000.

XIV. Approval Specifications

Directions for Use: See the labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling

Post Approval Requirements and Restrictions: see the Approval Order.

FocalSeal-L Synthetic Absorbable Sealant
Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

- **DESCRIPTION:**

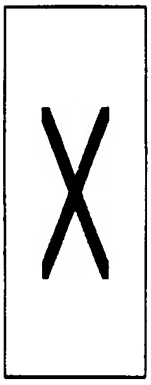
The FocalSeal-L Surgical Sealant system is comprised of synthetic absorbable sealant and primer solutions, two syringe/applicators, a light source, light wand and a PowerCap® light tester. The Sealant is formed via chemical and photochemical polymerization processes. The Sealant solution is provided in frozen form packaged in a red syringe and two primer vials. The two syringe applicators are used to deliver the primer and sealant solutions to the target tissue site. The FocalSeal reusable light source and light wand, ordered separately, photopolymerize the sealant solution to a thin film hydrogel. FocalSeal-L primer and sealant are aqueous solutions of poly (ethylene glycol) that have been modified with short segments of acrylate-capped poly (L-lactide) and poly (trimethylene carbonate). These solutions also contain buffers, initiators, and stabilizers (see section 8).

FocalSeal-L Surgical Sealant solutions (i.e., primer and sealant) are applied to the target tissue site as liquids. Upon exposure of the photo-initiator, Eosin-Y, to blue-green light, the primer and sealant solutions polymerize to form a crosslinked, clear, flexible, adherent hydrogel network. The sealant expands upon contact with body fluids and reaches its equilibrium swell volume within 24 hours. Over time the poly (L-lactide) and poly (trimethlyene carbonate) segments of FocalSeal-L Surgical Sealant degrade by hydrolysis, causing loss of mass and structural integrity. This results in the eventual dissolution and clearance of the Sealant via water-soluble molecules that are cleared through the kidneys or locally metabolized.

- **INDICATIONS:**

FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

Symbols



CE mark and identification number of notified body. Product conforms to the essential requirements of the Medical Device Directive. 93/42/EEC

See Instructions for Use

Batch Number

Method of Sterilization – Aseptic Fill Process

Method of Sterilization – Ethylene Oxide Gas

Temperature Indicator

Store ≤ -20°C
Use by year and month
Do not reuse/ resterilize
Fragile
Recycle
PowerCap light tester

Primer Vials
Red Sealant Syringe
Sealant Plunger
Primer/Sealant Applicators/Brushes
Primer Syringe/ Needle

- **CONTRAINDICATIONS:**

- FocalSeal-L Sealant is contraindicated for patients undergoing pneumonectomy or application over open or closed defects in main stem or lobar bronchi, due to an increased incidence of broncho-pleural fistulae observed in a clinical study in patients undergoing sleeve resection or bronchoplasty.

- FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.

- **WARNINGS:**
  - The incidence of thoracic wound infection in the pivotal study was 9/125 (7.2%) in FocalSeal-L and 2/55 (3.6%) in control patients. A similar trend for bronchial infection was observed in the European study. Monitor the patient for infection and take appropriate therapeutic action as needed.
  - The incidence of empyema in the pivotal study was 4/125 (3.2%) in FocalSeal-L and 0/55 (0%) in control patients. Monitor the patient for empyema and take appropriate therapeutic action as needed.
  - The incidence of cancer progression in the pivotal study was 13/125 (10.4%) in FocalSeal-L and 4/55 (7.3%) in control patients at 6 months post surgery. FocalSeal-L's effect on the incidence and progression of cancer in humans is not known beyond six months. In a long-term resorption study of 20 months, the incidence of tumors in rats was similar between FocalSeal-L and historical controls.
  - FocalSeal-L use has not been studied in non-elective pulmonary resection cases.
  - FocalSeal-L use has not been studied in contaminated or dirty pulmonary resection cases.
  - FocalSeal-L use has not been studied in the presence of active infection.
  - FocalSeal-L use has not been studied with other sealants or hemostatic materials.
  - The safety and effectiveness of FocalSeal-L has not been evaluated in humans under 18 years of age, pregnant or nursing women.
  - Possible explosion hazard if light source is used in presence of flammable anesthetics
  - Illuminated light wand can cause permanent damage if viewed directly with unprotected eye.
  - Avoid placing the light wand on the patient or on surgical drapes while the 40-second light cycle is activated. Inadvertent activation of the light source while the tip of the light wand is in close proximity with skin or surgical drapes may cause burns and/or ignition of combustible material.
  - To avoid excessive tissue heating, keep light wand approximately 2 cm from tissue surface.
  - FocalSeal-L resorption time in humans has not been evaluated. 35% of FocalSeal-L was present in rats after six months and the device was essentially resorbed at 20 months.

- **PRECAUTIONS:**
  - FocalSeal-L should not be used in persons who are hypersensitive to hydroquinone or any of the other device components (see section 8).
  - The safety of FocalSeal-L applications has not been evaluated in patients receiving more than 12.5 ml of primer or 39.0 ml of sealant.
  - In clinical studies effective sealing only required application of a thin (approx. 1 mm thick) layer of sealant to the target tissue site.
  - Use of additives (e.g., antibiotics) to the sealant has not been studied.
  - The sealant, primer, applicators and Power Cap are for single use only. DO NOT RE-STERILIZE.
  - The light wand must be cleaned and sterilized prior to use. (Please refer to Section 12 of the Light Source / Light Wand manual).
  - FocalSeal-L Sealant is light sensitive. Do not remove FocalSeal-L Sealant from red sealant syringe. Apply only as described in these Instructions for Use.
  - Inspect sterile package and seal prior to use. Do not use if sterile package or seal is damaged or open. Discard unused material.
  - Prior to application of FocalSeal-L Sealant, ensure that the surgical procedure is complete, hemostasis has been achieved, and the lung is deflated to the point of no active air leaks.
  - If FocalSeal-L Sealant is not prepared and applied as described in these Instructions for Use, the adherence and/or mechanical properties of the material may be compromised.
  - During application of FocalSeal-L Sealant, the lung should not be ventilated.
  - Brush/apply FocalSeal-L Sealant within primer area only.
  - Avoid pooling of primer material on the lung surface.
  - Do not create bubbles in sealant material during application. Bubbles may appear as end of sealant supply is reached. If this occurs, use new sealant syringe.
  - Keep the light wand tip approximately 2 cm away from tissue surface so that sealant solution receives adequate light exposure, and application site can be polymerized in one light cycle.

- Do not use any mixed FocalSeal-L primer or sealant more than 8 hours old, as the adherence and/or mechanical properties of the material may be compromised.

- **ADVERSE REACTIONS:**

  Adverse events which occurred in the FocalSeal-L cohorts at an incidence of 1% or greater in the US study and 2.9% or greater in European study are listed in Tables 1 and 2, respectively. The adverse events are listed in descending order according to frequency. These tables list all adverse events reported in the study including those attributed and not attributed to treatment.

Summary of Adverse Events for U.S. Study

Table 1

	FocalSeal-L (n=125)		*Control (n=55)*	
Event	#	%	#	%
Arrhythmia	29	23.2	17	30.9
Fevers	15	12.0	8	14.5
Cancer Progression	13	10.4	4	7.3
Pneumothorax	10	8.0	4	7.3
Thoracic Wound Infection	9	7.2	2	3.6
Pneumonia	9	7.2	5	9.1
Death	7	5.6	4	7.3
Confusion	7	5.6	0	0
Upper Respiratory Infection	7	5.6	3	5.5
Anemia	6	4.8	5	9.1
Ileus / Intestinal Obstruction	5	4.0	2	3.6
Urinary Tract Infection	4	3.2	3	5.5
Empyema	4	3.2	0	0
Persistent Atelectasis	4	3.2	0	0
Pulmonary Emboli	3	2.4	0	0
Deep Vein Thrombosis	3	2.4	0	0
Pleural Effusion	3	2.4	0	0
Residual Space	3	2.4	0	0
Colitis / Gastroenteritis	3	2.4	0	0
Hemoptysis	2	1.6	0	0
CHF	2	1.6	0	0
COPD	2	1.6	0	0
Anxiety	2	1.6	2	3.6
Hypotension	2	1.6	0	0

In the clinical trial, 7/125 FocalSeal-L and 4/55 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment. Regarding the severity of non-fatal adverse events, there were 66 severe events in 43 (34%) patients, 90 moderate events in 72 (58%) patients

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and 27 mild events in 13 (10%) in the 125 FocalSeal-L patients. In the 55 control patients there were 30 severe events in 17 (31%) patients, 41 moderate events in 28 (51%) patients and 15 mild events in 4 (7%) patients.

Summary of Adverse Events for European Study
Table 2

Event	*FocalSeal-L (n=34)*	*Control (n=26)*
Bronchial Fistulae [associated events included infection (4) and pneumothorax (2)]	8 (23.5%)	0 (0%)
Out of Range Lab Values	6 (17.6%)	2 (5.9%)
Pneumonia	5 (14.7%)	1 (3.8%)
Bronchial Infection	5 (14.7%)	0 (0%)
Superficial Phlebitis	4 (11.8%)	0 (0%)
Death	2 (5.9%)	1 (3.8%)
Metastatic Disease	2 (5.9%)	1 (3.8%)
DVT	2 (5.9%)	0 (0%)
Pneumothorax	2 (5.9%)	1 (3.8%)
Respiratory Depression / Insufficiency	2 (5.9%)	1 (3.8%)
Fever and Leukocytosis	1 (2.9%)	2 (7.7%)
Urinary Tract Infection	1 (2.9%)	2 (7.7%)
Pulmonary Infiltrates	1 (2.9%)	1 (3.8%)
Cardiac Failure	1 (2.9%)	1 (3.8%)
Cardiac Tamponade	1 (2.9%)	1 (3.8%)
Hematoma	1 (2.9%)	1 (3.8%)
Pulmonary Embolism	1 (2.9%)	1 (3.8%)
Anemia	1 (2.9%)	1 (3.8%)
Sepsis	1 (2.9%)	1 (3.8%)

The following events occurred in one FocalSeal-L patient, but no control patients: pulmonary erosion, post-thoracotomy syndrome, effusion, atelectasis, bronchitis, pulmonary edema, arrythmia, lymphedema, intestinal obstruction, visual field defect, CVA, and vomiting.

In the clinical trial, 2/34 FocalSeal-L and 1/26 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment

- **CLINICAL STUDIES:**

a) U.S. Study

An open label, prospective, randomized, multi-center study comparing standard tissue closure techniques (control) to standard tissue closure techniques plus the FocalSeal-L Sealant (treatment) in a total of 180

eligible patients scheduled to undergo elective pulmonary resections via an open thoracotomy procedure. Application of FocalSeal-L Sealant to the bronchial stump was contraindicated in this study. Patients were randomized to treatment or control in a 2:1 ratio and the first two treatment patients were prospectively identified as pilot patients and not included in the effectiveness analysis.

The primary efficacy endpoint was the proportion of patients determined to be air leak free at the end of the surgical procedure and who remained air leak free through hospital discharge. The secondary efficacy endpoints were mean time to air leak cessation and the proportion of patients air leak free at the end of the surgical procedure. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1, 3 and 6 months post-operatively.

Patient and Baseline Characteristics are presented in Table 3.

Patient and Baseline Characteristics[1]

Table 3

		FocalSeal-L (n=125)	Control (n=55)
Gender	Female	73 (58%)	24 (44%)
	Male	52 (42%)	31 (56%)
Age at Surgery (yrs)	Mean	62.1	62.1
	Range	31 – 75	21 - 75
	Std. Dev.	9.7	10.0
Primary Surgical Diagnosis	Pulmonary Cancer	90 (72%)	43 (78%)
	Pulmonary Metastasis	16 (13%)	7 (1%)
	Benign Neoplasis	8 (7%)	2 (4%)
	Other	11 (9%)	3 (5%)
Types of Surgery	Single Lobectomy	83 (66%)	28 (51%)
	Single Wedge	18 (14%)	7 (13%)
	Segmentectomy	8 (7%)	6 (11%)
	Bi-Lobectomy	8 (7%)	4 (7%)
	Other	8 (7%)	10 (18%)
Number of Patients with Air Leaks Prior to Randomization		95 (76%)	39 (71%)

[1]No statistically significant ($p<0.05$) differences were detected between groups.

The results of the US study are presented in Table 4.

Study Endpoint Results

Table 4

	FocalSeal-L (n=117)	Control (n=55)	p-Value
Patients Air Leak-Free through Hospital Discharge	39% (46/117)	11% (6/55)	0.001[1]
Patients Air Leak-Free at Skin Closure	92% (108/117)	29% (16/55)	0.001[1]
Time to Air Leak Cessation (Hrs)			0.006[2]
Mean (SE)	30.9 (4.8)	52.3 (11.6)	
Median	12.1	27.6	

[1] Mantel-Haenszel Test
[2] Generalized Wilcoxon Test comparing time to last air leak distribution

Analyses of additional data collected in the study are summarized in Table 5.

Additional Analyses

Table 5

	FocalSeal-L (n=125)	Control (n=55)	p-Value[1]
Days to Chest Tube Removal			
Mean (SE)	4.5 (0.2)	5.2 (0.5)	NS[1]
Median	4.0	4.0	
Days to Hospital Discharge			
Mean (SE)	7.4 (0.4)	10.1 (1.8)	
Median	6.0	6.0	NS
Days to Drainage < 125 cc/day			
Mean (SE)	3.4 (0.12)	3.7 (0.25)	NS
Median	3.0	3.0	
Patients with Recurrent Air Leak[2]	62/108 (57%)	10/16 (63%)	NS

[1] NS – Not statistically significant.
[2] In patients who were air leak free at skin closure, but subsequently developed a post-operative air leak, 93% and 90% of the air leaks in FocalSeal-L and Control patients, respectively, began within 24 hours after surgery.

b) European Study
This was an open label, prospective, randomized (1:1), multi-center study to compare standard tissue closure techniques (control; n=26) to standard tissue closure techniques plus FocalSeal-L Sealant (treatment; n=34) in a total of 60 eligible patients scheduled to undergo pulmonary resections.

The primary efficacy endpoint was the proportion of patients air leak free at the end of the surgical procedure. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1 and 2 months post-operatively.

The study population was predominantly male (70% of treatment group and 77% of control group) and the primary surgical diagnosis was bronchogenic carcinoma (77% of treatment group, 85% of control group). The primary surgical procedure was single lobectomy (83% of treatment group, 77% of control group).

The proportion of patients air leak free at the end of the surgical procedure was 100% in the treatment group and 27% in the control group (p=0.001).

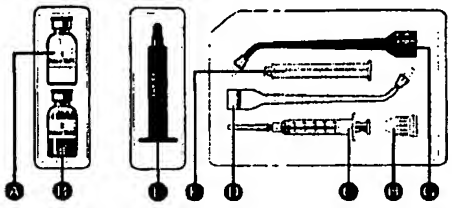
8) INSTRUCTION FOR USE:

Introduction
FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection by placing a thin, adherent coating of a biocompatible and absorbable hydrogel onto tissue. Applied as a liquid, the FocalSeal-L Sealant flows and conforms to the target tissue site and is then chemically and photochemically polymerized to form a flexible, adherent hydrogel.

FocalSeal-L Sealant contains polymerizable macromers, composed of poly (ethylene glycol) modified with biodegradable and photo-reactive elements. The FocalSeal-L Sealant is formed by *in situ* polymerization of two aqueous pre-polymer solutions applied in 3-step process. In the first step, the primer solution is brushed onto the target site using the designated primer applicator. This step provides coverage of the tissue surface and facilitates flow of the low viscosity primer solution into the tissue interstices defined by the target surface topography. In the second step, the sealant solution is brushed onto the target tissue site using the sealant applicator. This step provides mixing of the sealant and primer solutions. In the third step, the sealant brush tip is removed and the sealant is applied directly over the target site in a continuous manner, allowing the sealant to flow in an uninterrupted layer approximately 1 mm thick, which is then illuminated with visible light

of a specified filtered wavelength by the light wand. This step provides photopolymerization, which completes the crosslinking of the primer and sealant molecules and results in formation of an adherent, flexible sealant.

HOW SUPPLIED:



Single-Use: All items are sterile.

One Frozen Material Set Containing:

One blister pack containing:

A. One Primer Vial 1 - 5 ml of a yellow solution material containing: fructose, ferrous gluconate and water for injection

B. One Primer Vial 2 - a pink solid lyophilized material containing: primer macromer, NaCl and Eosin Y

One blister pack containing:

E. One Red Sealant Syringe - 8 ml of FocalSeal-L Surgical Sealant, a pink viscous liquid, containing: sealant macromer, triethanolamine, KH_2PO_4, vinyl caprolactam, t-butyl hydroperoxide, Eosin Y, hydroquinone and water for injection

One Applicator Kit Containing:

C. One 5 ml syringe with a 16-gauge needle

D. One Primer applicator with brush

G. One Sealant applicator with brush

F. One plunger

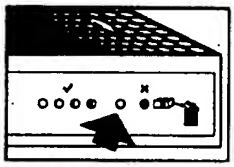
H. One PowerCap light tester

Reusable: Items are supplied non-sterile.

- One non-sterile, reusable light wand.
- One non-sterile, reusable light source and power cord.

Storage:

- Store the FROZEN FocalSeal-L Surgical Sealant and Primer in the material box at ≤ -20°C to maintain performance and keep its useful shelf life. Do not use after expiry date.
- A temperature indicator strip on the side of the frozen material box should be checked prior to use, to ensure that product has been stored at the appropriate temperature.



PRECAUTION:

- If the window on the indicator strip has turned completely blue, do not use. Discard the package and retrieve another frozen material set from the freezer.

- Applicator kit, light wand, and light source do not require any special storage conditions.

Sterility:

- Contents of material box and applicator kit are supplied sterile. FocalSeal-L Sealant and Primer are sterilized by aseptic fill processes. The FocalSeal applicator kit is sterilized by ethylene oxide gas.
- Do not use if sterile package is damaged or opened. Discard any unused material following the surgical procedure.
- The light wand is supplied non-sterile and must be cleaned and sterilized prior to use. Refer to the Light Source/Light Wand Instructions for Use.
- The light source is supplied non-sterile. Both light wand and light source are reusable.

Light Source / Light Wand Preparation

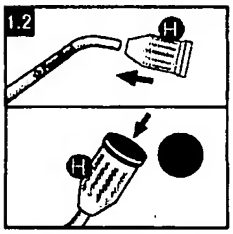
Note:

- *Do not remove PowerCap light tester during illumination cycle.*
- *To avoid inaccurate test results, wait 2 minutes between initial and repeat light source/light wand output tests.*
- *If the PowerCap light tester is not available, measure the light system output with an optical power meter (refer to the Light Source/Light Wand Instructions for Use).*

1.1 Turn the FocalSeal light source on five minutes prior to use. Refer to the FocalSeal Light Source/Light Wand Operating Instructions manual for complete description, warning and cautions.

Check that both the distal tip optical window and the optical connector of the light wand are clean prior to use of the PowerCap light tester.

1.2 Fully push the PowerCap light tester onto the distal end of the FocalSeal light wand. Turn light wand on for one complete (40 second) cycle. (Fluted sides of the tester illuminate blue during the light cycle.) Within one complete light cycle, a small colored circle will appear in the center of the black disk, at the end of the PowerCap light tester. Appearance of a colored circle indicates that the light source/light wand combination has sufficient light output and is ready for use. Remove the tester from the light wand prior to use in the surgical procedure.



If the colored circle does not appear on the black disk of the PowerCap light tester by the end of the complete light cycle, wait 2 minutes, then repeat test procedure. If the colored circle does not appear after the second light cycle, repeat the test procedure with a new light wand. If the test still fails, refer to the Troubleshooting section of the FocalSeal Light Source/Light Wand Operating Instructions.

Keep the PowerCap light tester available in the sterile field for additional intra-operative light output tests. Do not discard until procedure is complete.

FocalSeal-L Material Preparation:

Note: Allow 10 minutes for material preparation.

2.1 If the window on the indicator strip has turned completely blue, do not use. Discard the package and retrieve another frozen material set from the freezer.

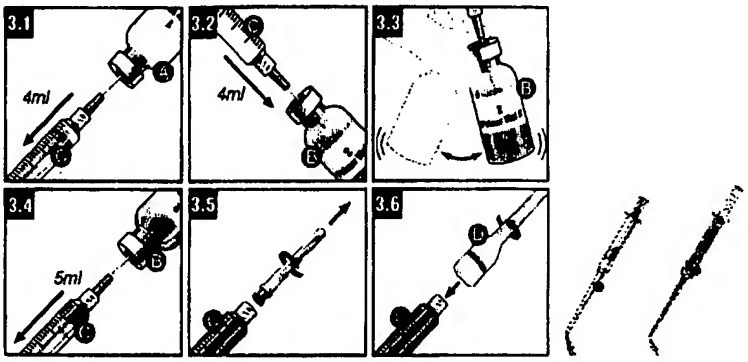
PRECAUTION:

- Do not thaw Primer Vial 2 in warm sterile saline.

FocalSeal-L Primer and Sealant Preparation:

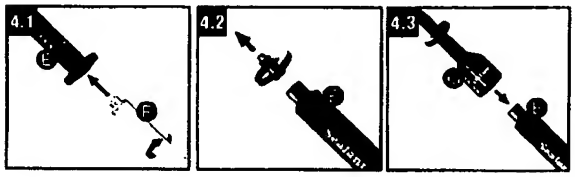
2.2 Thaw the FocalSeal-L Primer solution Vial 1 and the FocalSeal-L Sealant syringe. If Vial 1 is not thawed upon opening, place Primer Vial 1 into a pan filled with warm sterile saline. (Approximately 6 minutes in warm saline bath or approximately 45 minutes at room temperature).

Primer Preparation:



Note: The primer has a white applicator and the sealant has a black applicator. Take care to connect the proper applicator to the appropriate syringe.

Sealant Preparation:



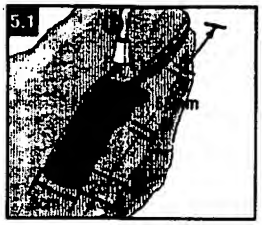
Target Site Preparation:

1. Prior to application of FocalSeal-L Sealant, ensure that the surgical procedure is complete and hemostasis has been achieved. 2. Rinse the area to be treated with saline and remove any pooled blood or blood clots with irrigation and/or suction. 3. Ventilation of the target area should be stopped. If patient needs to be ventilated, a reduced tidal volume is recommended to minimize lung movement and active air leakage during application.
4. Maximum area for single application of primer/sealant is 3 cm diameter or 55 mm linear staple line. For areas larger than this, apply in stages. Clean brushes with sterile saline between applications.

- **FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.**

Note: If target site is vertical, allow suction to provide drainage at lowest point of target field, to ensure that primer or other fluids do not pool when sealant solution is being applied.

Primer Application:

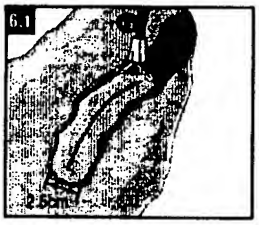


5.1 Apply primer solution sparingly through applicator while brushing the target surface. Ensure complete but thin distribution up to a minimum of 1 cm margin around the perimeter of the target site. Apply sufficient primer to coat the target site, while avoiding pooling and bubbling of primer material on the surface.

FocalSeal-L Surgical Sealant Application:

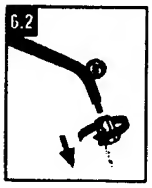
Note: If more than 30 seconds elapses between the application of primer and application of sealant, rinse treated area with saline and re-apply primer before applying sealant.

6.1 Apply a few drops of sealant through the applicator, then briefly brush the surface of the target tissue using the sealant applicator brush to spread sealant evenly and blend the sealant within primed area only.

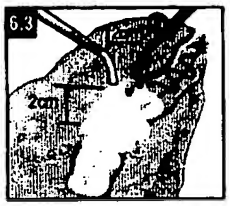


Note: The brush should be cleaned during the sealing cycle. Proper brush cleaning can be accomplished by removing any excess material, which might build up during the sealing cycle, using a dry or dampened gauze sponge. Repeat brush-cleaning steps as necessary between uses during the sealing process. Brush can be cleaned repeatedly in this manner without disturbing the brush and bristle integrity.

- Remove the sealant brush tip and apply sealant directly over the target site.



- Apply an uninterrupted layer of sealant, approximately 1 mm thick, in a continuous serpentine manner. Do not apply the sealant solution beyond the primed area. After the sealant has spread onto the target surface to form a thin laminating layer, expose the sealant to one complete 40-second light cycle using the Light Source/Light Wand. The tip of the Light Wand should be positioned perpendicular to and approximately 2 cm above the surface of the sealant.



PRECAUTION:

- Keep the light wand tip approximately 2 cm away from tissue surface so that sealant solution receives adequate light exposure, and application site can be polymerized in one light cycle.

Note: The activated light wand should follow the applicator as sealant solution is being dispensed, but not so closely that the sealant prematurely gels before it can spread. This can be accomplished by maintaining a distance of approximately 2 cm between the center of the illuminated area and the applicator tip.

- Bubbles may appear as end of sealant solution supply is reached. Avoid bubbles in sealant material during application in order to ensure maximum integrity of the sealant.
- Do not allow the light wand tip to contact tissue, tissue fluid, sealant solution or primer solution, as the residue from these materials may compromise the light output of the wand. If the tip becomes contaminated with a foreign substance, clean with sterile saline and wipe with dry gauze to maintain maximum light output.

7. If the target site is sealed in segments, repeat step 5.1 through 6.3 by allowing a minimal (0.5cm) overlap in application segments.

Re-application:

1. Visually inspect the area for full sealant coverage. If a site is not properly sealed, remove any detachable sealant material with sharp dissection, re-prime and apply sealant as outlined in step 5.1 through 6.3, in a slightly wider perimeter if necessary.
2. Ensure that no sutures or suture tails are sticking through the sealant material. If a suture protrudes and therefore is not properly covered, deposit enough sealant material only to cover the suture material. Alternatively, trim the tails to a shorter length, and reapply sealant.

Note: Primer is necessary only at tissue interface, and need not be used when depositing additional sealant to the initial sealant layer.

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